DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-356/S003

Gilead Sciences, Inc
Attention: Alan S. Taylor, PhD
Vice President, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Taylor:

Please refer to your supplemental new drug application dated October 14, 2002 and received October 15, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIREAD® (tenofovir disoproxil fumarate)) 300mg Tablets.

We acknowledge receipt of your submissions dated:

October 17, 2002	June 4, 2003	July 15, 2003	August 11, 2003
March 13, 2003	June 16, 2003	July18, 2003	August 12, 2003
May 2, 2003	June 30, 2003	July 25, 2003	August 13, 2003
May 6, 2003	July 3, 2003	August 6, 2003	August 14, 2003
May 15, 2003	July 9, 2003	August 8, 2003	

This supplemental new drug application provides for the use of VIREAD® (tenofovir disoproxil fumarate) 300mg Tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of VIREAD in treatment-naïve adults and in treatment-experienced adults.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert) dated August 14, 2003.

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved supplement NDA 21-356/S-003**". Approval of submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated August 14, 2003. These commitments are listed below.

1. Investigate the effect of calcium and vitamin D supplementation in the 96-week extension of Study GS-99-903 (*i.e.* from three to five years).
   Protocol Submission: October 2003
   Study Start: December 2003
   Final Report Submission: October 2006

2. Evaluate the safety of TDF in patients with renal impairment using the new dosing recommendations over 48 weeks. The study will include assessments for potential bone and renal toxicity.
   Protocol Submission: December 2003
   Study Start: July 2004
   Final Study Submission: July 2007

3. Extend Study GS-00-903 as a single arm, open-label study in a subset of study sites for two additional years with monitoring of bone densitometry (but without biochemical markers of bone turnover).
   Protocol Submission: September 1999
   Study Start: June 2000 (144-week clinical study report July 2004)
   Final Study Submission: October 2006 (including two-year extension data)

4. Investigate possible mechanisms of drug interactions between tenofovir and the nucleosides, didanosine and abacavir, and the protease inhibitor, atazanavir, using *in vitro* techniques. As these studies will involve a variety of techniques, submit interim results as they become available.
   Protocol Submission: December 2003
   Study Start: March 2004
   Final Study Submission: December 2004

5. Conduct a study to assess the *in vitro* antiviral activity of tenofovir against HIV-2.
   Final Study Submission: October 2003

In addition to the formal postmarketing commitments listed above, you have agreed to the following informal agreements with the Division in your submission dated August 14, 2003.

- Develop educational materials for clinicians and patients regarding the value and appropriate use of calcium and vitamin D supplementation with tenofovir therapy, pending the results of the 96- week extension of study 903. Submission Date: October 2006

- Submit an update on the progress with investigations of virologic failure in triple nucleoside regimens containing tenofovir. Submission Date: October 2003

We also remind you of the Pediatric Written Request issued on December 21, 2001.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final study reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, the number of patients entered into each study. All submissions, including supplements relating to these

postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Marsha Holloman, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra B. Birnkrant, MD
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure Final Printed labeling (product package insert and patient package insert)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
8/15/03 03:49:45 PM
NDA 21-356